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| 08/913,555 | 09/19/1997 | NOBUHIKO KAYAGAKI | 715-118 | 7102 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/913,555 | KAYAGAKI ET AL. | |
| | Examin r | Art Unit | |
| | Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 July 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *51-62,73-75 and 154* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-62,73-75 and 154* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. Claims 51-62, 73-75, and 154 are pending and are being acted upon in this Office Action.

2. The following are new grounds of rejections.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 51-62, 73-75 and 154 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not teach how to make and use *any* monoclonal antibody or *any* "active fragment" thereof that specifically reacts with *any* "**Fas ligand**" as set forth in claims 51-57, (2) a method of detecting *any* Fas ligand using *any* monoclonal antibody or active fragment thereof as set forth in claim 58-60, (3) *any* kit for use in detecting any Fas ligand using a combination of a plurality of monoclonal antibodies against Fas ligand as set forth in claims 61-62 and (4) a method of producing *any* monoclonal antibodies which reacts with *any* Fas ligand as set forth in claims 73-75 and 154 for detection assay because there is insufficient guidance as to the biochemical structure such as the amino acid sequence of any other Fas ligand.

The specification discloses only three Fas ligand from human, mouse and rat (See page 2-3 of specification). The specification discloses five monoclonal antibodies that bind specifically to human Fas ligand which produced by hybridoma FERM BP-5044, FERM BP-5045, FERM BP-5046, FERM BP-5047, and FERM BP-5048. The monoclonal antibodies produced by the hybridoma mentioned above have the binding specificity of SEQ ID NO: 31 and inhibit apoptosis of Fas expressing cells at a concentration of 0.01-8 μg more than the control Fas-Ig chimera molecule at the same concentration. The specification further discloses a monoclonal antibody that binds specifically to mouse Fas ligand produced by hybridoma BP-5334 for immunoaffinity chromatography and detection assays.

Although the specification discloses Fas ligand from human, mouse and rat, the incorporation of essential material in the specification by reference to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The attempt to incorporate subject matter into this application by reference to journal paper is improper because the Fas ligand is essential material for making the claimed monoclonal antibodies. Further, mere reference to another publication is not an incorporation of anything therein into the application containing such references for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144, (CCPA 1973).

Even if the amino acid sequence of the Fas ligand is properly incorporated into the specification, the specification discloses only three amino acid sequences of Fas ligands from mouse, human and rat. There is insufficient guidance as to the structure such as the amino acid sequence (epitope) of other Fas ligand to which the monoclonal antibody binds. There is also insufficient guidance as to the immunogen (the specific amino acid sequence used by Applicants) to make monoclonal antibody that reacts to other undisclosed Fas ligand wherein the antibody can inhibit the apoptotic function more than any Fas-Ig chimera molecule by at least 90% as determined by the survival rate of target cells.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are

critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Given the indefinite number of undisclosed "Fas ligand", it is unpredictable which undisclosed "Fas ligand" and fragment thereof can generate monoclonal antibodies that would bind not only specifically to Fas ligand from human, mouse or rat abut also would inhibit the apoptotic function of soluble Fas receptor such as Fas-Ig chimera molecule by at least 90%.

Further, the specification discloses only five monoclonal antibodies that bind to human Fas ligand and one monoclonal antibody that binds specifically to mouse Fas ligand wherein said monoclonal antibodies are produced by the specific hybridoma such as FERM BP-5044, FERM BP-5045, FERM BP-5046, FERM BP-5047, and FERM BP-5048, and BP-5334. Even if the claims are limited to the specific hybridoma mentioned above, it is apparent that said hybridoma FERM BP-5044, FERM BP-5045, FERM BP-5046, FERM BP-5047, and FERM BP-5048, and BP-5334 are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit throughout the life of the patent.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which case the statement need not be verified. See MPEP 1.804 (b).

Although a Deposit Receipt of FERM BP-6909 and a statement through the undersigned attorney of record that the cell line will be irrevocably and without restriction and condition released to the public upon issuance of the a patent that has been submitted in 1/13/00, it is noted that the Deposit Receipt referred to HFAS/WR19L cell line (Fas transfected cell line) and not the specific hybridoma mentioned above.

Since the amino acid sequence of *any* Fas ligand and the binding specificity of *any* monoclonal antibody that bind to any Fas ligand are not enabled, it follows that the method of making any monoclonal antibodies or any active fragment thereof that specifically reacts with *any* Fas ligand and has the property of inhibiting apoptosis is not enabled. It also follows that the method of detecting any Fas ligand using any undisclosed monoclonal antibodies against any undisclosed Fas ligand is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

5. Claims 51-62, 73-75 and 154 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* monoclonal antibody or active fragment thereof that specifically reacts with *any* "Fas ligand" as set forth in claims 51-57, (2) a method of detecting *any* Fas ligand using *any* monoclonal antibody or active fragment thereof as set forth in claim 58-60, (3) *any* kit for use in detecting any Fas ligand using a combination of a plurality of monoclonal antibodies against Fas ligand as set forth in claims 61-62 and (4) a method of producing *any* monoclonal antibodies which reacts with any Fas ligand as set forth in claims 73-75 and 154 for detection assay for the following reasons.

The specification discloses only three Fas ligand from human, mouse and rat (See page 2-3 of specification). The specification discloses five monoclonal antibodies that bind specifically to human Fas ligand which produced by hybridoma FERM BP-5044, FERM BP-5045, FERM BP-5046, FERM BP-5047, and FERM BP-5048. The monoclonal antibodies produced by the hybridoma mentioned above have the binding specificity of SEQ ID NO: 31 and inhibit apoptosis of Fas expressing cells at a concentration of 0.01-8 μg more than the control Fas-Ig chimera

molecule at the same concentration. The specification further discloses a monoclonal antibody that binds specifically to mouse Fas ligand produced by hybridoma BP-5334 for immunoaffinity chromatography and detection assays.

With the exception of the specific monoclonal antibodies that bind to the specific Fas ligand such as human, mouse and rat, there is insufficient written description about the structure associated with function of any Fas ligand to which the claimed monoclonal antibody binds, much less inhibiting apoptosis more than a control Fas-Ig chimera molecule.

Given the lack of a written description of *any* additional representative species of Fas ligand to which the antibody binds, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 53, 55, 73 and 154 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "or an active fragment thereof" in claim 53, line 2, claim 55, line 2, and claim 73, line 2, is ambiguous because it is not clear if the active fragment is referred to the binding fragment of the antibody or the active fragment of the Fas ligand to which the antibody binds. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. The "or not using, as an indicator, ...of Fas ligand-expressing cell against Fas-expressing COS cells against Fas-expressing cells," in claim 154 (5) and claim 73 (5) is ambiguous and non-sense which require deletion. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. Further, The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a

foreign document and are replete with grammatical and idiomatic errors. Appropriate correction is required.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 51-60, 73-75 and 154 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi *et al* (International Immunology 6(10): 1567-74, June 1994; PTO 892) or Suda *et al* (Cell 75: 1169-78, December 1993; PTO 892) each in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 92-94, pages 116-117, pages 626-629) or Campbell *et al* (in Monoclonal Antibody Technology, 1984, Elsevier Science Publisher, New York, NY, page 1-32; PTO 892).

Takahashi *et al* teach various Fas Ligands such as human FasL, mouse FasL and rat FasL (See page 1571, in particular). Takahashi *et al* teach cells such as COS cells transfected with the reference Fas ligand to induce apoptosis in cells expressing the Fas receptor such as WR19L cells that have been transfected with the Fas cDNA for (See page 1571, Figure 4, page 1570, Assay of cytotoxicity activity, in particular). Takahashi *et al* teach that apoptotic (cytotoxic) effect of the human and mouse Fas ligand (FasL) is compared to the soluble forms of mouse Fas (mFas-Fc) or human Fas (hFas-Fc) by expressing the hybrid gene consisting of the extracellular region of mouse or human Fas fused to the Fc region of the human Ig heavy chain (IgH) to form a chimera molecule (Fas-Ig) (See page 1570, column 1, assay of cytotoxic activity, in particular). Takahashi

*et al* teach the use of cell line such as WR19L cell expressing the mouse Fas (W4) or human Fas (WC8A) for use as target cells (See page 1570, column 1, in particular). Takahashi *et al* teach the interaction of FasL on the effector cells with Fas on the target cells induces an apoptotic signal in the target cells (See page 1573, column 1, in particular). The reference amino acid sequence of human FasL which is a death factor expressed in cytotoxic T lymphocytes (CTL) and its corresponding cDNA is an important tool which can be use to elucidate the pathological role of FasL I human disease (See page 1573, column 2, in particular).

Suda *et al* teach that a recombinant Fas ligand from rat that induces apoptosis and mice carrying mutations homozygous at the lpr locus have a defect in apoptosis due to non-functional Fas receptor while mice carrying a point mutation in the gld locus have a defect in apoptosis due to the nonfunctional Fas ligand (See page 1169, Figure 2, page 1175, column 1, in particular). Suda *et al* further teach a method of making a Fas ligand-expressing cell such as Cos cells and d10S transfected with Fas Ligand cDNA (See page Fig 1, materials and methods, in particular). The reference Fas ligand expressing cells induces apoptosis in cells expressing the Fas receptor such as W4 cells that has been transfected with the Fas antigen (See page 1171, column 2, in particular). Suda et al teach that the soluble form of the Fas ligand actively triggers apoptosis by binding to Fas (See page 1174, column 2, second full paragraph, in particular).

The claimed invention as recited in claim 51 differs from the teachings of the references only that the monoclonal antibody inhibits apoptosis more than a control Fas-Ig chimera molecule.

The claimed invention as recited in claim 52 differs from the teachings of the references only that the monoclonal antibody inhibits apoptosis at a concentration of 0.1-8 μg/ml more than the Fas-Ig chimera molecule at the same concentration.

The claimed invention as recited in claim 53 differs from the teachings of the references only that the monoclonal antibody or active fragment thereof which specifically reacts with a Fas ligand can inhibit apoptosis by at least 90%, as determined by the survival rate of Fas-expressing target cells in a culture supernatant containing 12-fold dilution of soluble Fas ligand, in 100 μl in 96-well plate after 16 hours.

The claimed invention as recited in claim 54 differs from the teachings of the references only that the monoclonal antibody or active fragment thereof which specifically reacts with a Fas ligand wherein the survival rate of the Fas transfected target cells (Fas/WR19L) can be enhanced to at least 90% when the soluble Fas ligand is added to the 12 fold dilution of the culture

supernatant of the Fas ligand gene-transfected cells as effector molecule in an amount of 25 μl at 37 °C for 16 hours.

The claimed invention as recited in claim 55 differs from the teachings of the references only that the monoclonal antibody or the active fragment thereof which specifically reacts with a Fas ligand can inhibit a physiological reaction of a human Fas ligand but the mouse Fas ligand.

The claimed invention as recited in claim 56 differs from the teachings of the references only that the monoclonal antibody or the active fragment thereof which specifically reacts with a Fas ligand which can affinity-purify a soluble Fas ligand present in a culture supernatant of Fas ligand-expressed cells.

The claimed invention as recited in claim 57 differs from the teachings of the references only that the monoclonal antibody or the active fragment thereof which specifically reacts with a Fas ligand which can immunoprecipitate Fas ligand molecules on Fas ligand-expressed cell surface or soluble Fas ligand molecules secreted in a culture solution.

The claimed invention as recited in claim 58 differs from the teachings of the references only that method of detecting a Fas ligand in solution is by using a plurality of monoclonal antibodies against Fas ligand.

The claimed invention as recited in claim 59 differs from the teachings of the references only that the method of detecting a Fas ligand in solution uses a plurality of monoclonal antibodies against Fas ligand wherein the antibody is immobilized on a carrier and wherein the monoclonal antibody is labeled.

The claimed invention as recited in claim 60 differs from the teachings of the references only that the method of detecting a Fas ligand in solution uses a plurality of monoclonal antibodies against Fas ligand wherein the IgM type monoclonal antibody is immobilized on a carrier and the Fas ligand in solution is detected by a biotin-labeled monoclonal of IgG type.

The claimed invention as recited in claims 73 and 154 differs from the teachings of the references only that the monoclonal antibody or a active fragment thereof which specifically reacts with a Fas ligand is produced by a process comprising the steps of immunizing an animal that does not express a functional Fas molecule with a Fas ligand molecule or a Fas ligand expressing cells, isolating the antibody producing cells from the animal, fusing the antibody producing cells with myeloma cells, culturing the hybridoma cells and isolating monoclonal antibody form the supernatant of the hybridoma.

The claimed invention as recited in claim 74 differs from the teachings of the references only that the method of producing monoclonal antibody or a active fragment thereof which specifically reacts with a Fas ligand wherein the mouse is a rodent belonging to MRL lpr/lpr mice.

The claimed invention as recited in claim 75 differs from the teachings of the references only that the method of producing monoclonal antibody or a active fragment thereof which specifically reacts with a Fas ligand wherein the mouse is a rodent belonging to MRL gld mice.

Harlow *et al* teach a method of producing monoclonal antibody produced by a hybridoma or cell line that binds to any antigen wherein the reference method comprises the steps of immunizing the animal such as a rodent with an antigen of interest, isolating the antibody producing cells from the animal, fusing the antibody producing cells with myeloma cells, culturing the hybridoma cells and isolating monoclonal antibody form the supernatant of the hybridoma (See page 145-149, in particular). Harlow *et al* teach that the antibodies from serum or ascites can be purified using conventional methods involving precipitation and column chromatography (See page 289, in particular) and IgM type monoclonal antibody is immobilized on a carrier such as DEAE for purification purpose because of its multivalent (See page 296-297, in particular). Harlow *et al* further teach a method of producing antibody fragment (active fragment) wherein the fragment is Fab fragment (See page 626-629, in particular). Harlow *et al* teach that the problems of using multivalent antibodies (IgM) on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). Harlow *et al* also teach labeling any antibody with various labels such as enzyme (See chapter 9, in particular) for various detection assays. The advantages of enzyme labeling are longer shelf life, and higher sensitivity (See page 322, in particular). Harlow *et al* teach a method of labeling antibodies with biotin. The advantage of labeling antibodies with biotin is that it increases the sensitivity of detection due to the multimeric avidin and streptavidin that form complex with biotin and thus increases the strength of the signal (See page 340-341, in particular). Harlow *et al* teach that the advantages of monoclonal antibody are their binding specificity, their homogeneity and their ability to be produced in unlimited quantities by hybridoma (See page 141, last full paragraph, in particular).

Campbell *et al* teach that "it is customary now for any group working on a macromolecule to both clone the gene encoding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (See page 29, section Basic Research,

in particular). Campbell *et al* further teach conventional antiserum which is polyclonal antibody (See page 4, comparison of monoclonal antibodies and conventional antiserum, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce monoclonal antibody or binding fragment (active fragment) as taught by Harlow et al or Campbell that is specific for Fas ligand from human, rat or mouse as taught by Takahashi *et al* or Suda *et al* by immunizing a mouse lacking functional Fas such as lpr mice or mouse lacking functional Fas ligand as taught by Suda *et al* with the human Fas ligand or the human Fas ligand expressing cells as taught by the Takahashi et al. It would be been obvious to one having ordinary skill in the art at the time the invention was made to screen for inhibitor of apoptosis more than the control Fas-Ig chimera molecule using the Fas ligand transfected cell line as effector molecule and Fas expressing cell line as the target cells as taught by the Suda *et al* and Takahashi *et al.* It would be been obvious to one having ordinary skill in the art at the time the invention was made to detect Fas ligand in any solution using the monoclonal antibody or binding fragment (active fragment) as taught by Harlow et al or Campbell that is specific for Fas ligand from human, rat or mouse as taught by Takahashi *et al* or Suda *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to generate monoclonal antibodies to the claimed polypeptide based on the fact that it is a conventional practice in the art to do so for further study, characterization and identification of a polypeptide as taught by Campbell *et al* since the antibody to the Fas Ligand would interfere with the interaction between Fas ligand and its Fas receptor and thereby would inhibit the physiological function such as apoptosis as taught by Suda *et* and Takahashi *et al.* Harlow *et al* teach that the advantage of monoclonal antibody are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Takahashi *et al* teach that the amino acid sequence of human FasL which is a death factor expressed in cytotoxic T lymphocytes (CTL) and its corresponding cDNA are important tool in which can be use to elucidate the pathological role of FasL I human disease (See page 1573, column 2, in particular). Suda *et al* teach that a recombinant Fas ligand from rat that induces apoptosis and mice carrying mutations homozygous at the lpr locus have a defect in apoptosis due to non-functional Fas receptor while mice carrying a point mutation in the gld locus have a defect in apoptosis due to the

nonfunctional Fas ligand (See page 1169, Figure 2, page 1175, column 1, in particular). Claim 51 is included in this rejection because it is within the purview of one ordinary skill in the art at the time the invention was made to screen for inhbitor of apoptosis more than the control by comparing to a control such as Fas-Ig chimera molecule as taught by Takahashi *et al* who teach that apoptotic (cytotoxic) effect of the human and mouse Fas ligand (FasL) is compared to the soluble forms of mouse Fas (mFas-Fc) or human Fas (hFas-Fc) by expressing the hybrid gene consisting of the extracellular region of mouse or human Fas fused to the Fc region of the human Ig heavy chain (IgH) to form a chimera molecule (Fas-Ig) (See page 1570, column 1, assay of cytotoxic activity, in particular). Claim 52 is included in this rejection because it is within the purview of one ordinary skill in the art at the time the invention was made to compare apoptosis induced by any agent by having equal or the same concentration such as 0.01-8 μg/ml as the soluble Fas-Ig chimera molecule as taught by Takahashi *et al.* Claim 53 is included in this rejection because it is within the purview of one ordinary skill in the art at the time the invention was made to screen for inhbitor of apoptosis more than the control such as at least 90% as determined by rate of survival of Fas-transfected target cells as taught by the Suda *et al* and Takahashi *et al.* The use of soluble Fas ligand as an effector molecule in claims 53 and 54 is within the teaching of the Suda et al who teach that the soluble form of the Fas ligand actively triggers apoptosis by binding to Fas (See page 1174, column 2, second full paragraph, in particular). The recitation of 12-fold dilution of soluble Fas ligand and the arbitrary time point such as 16 hours at 37°C after exposing the target cells to the soluble Fas ligand or apoptotic inducing agent in 96-well plate at 100 μl are within the purview of one ordinary skill in the apoptosis field as taught by Suda *et al* and Takahashi *et al* (See cytotoxicity assays, in particular). Claims 56 and 57 are included in this rejection because a product is a product, irrespective what its intended use.

11. Claims 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi *et al* (International Immunology 6(10): 1567-74, June 1994; PTO 892) or Suda *et al* (Cell 75: 1169-78, December 1993; PTO 892) each in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 92-94, pages 116-117, pages 626-629) or Campbell *et al* (in Monoclonal Antibody Technology, 1984, Elsevier Science Publisher, New York, NY, page 1-32; PTO 892) as applied to claims 51-60, 73-75 and

154 mentioned above and further in view of US Pat No 4,950,588 A (August 21, 1990, PTO 892).

The combined teachings of Takahashi *et al*, Suda *et al*, Harlow *et al* and Campbell *et al* have been discussed supra.

The claimed invention as recited in claim 61 differs from the teachings of the reference only a kit comprising Fas ligand monoclonal antibody for use in detecting a Fas ligand.

The claimed invention as recited in claim 62 differs from the teachings of the reference only a kit for use in detecting a Fas ligand in the blood of a person attacked by infectious mononucleosis, systemic lupus erythematodes or hepatitis.

The '588 patent teaches a test kit for conducting chemilumininescence assays comprising in a containers the necessary ingredient such as a chemiluminescence precursor, an enzyme and antibody that for detecting nucleic acid, antibodies, antigens, or enzymes in a sample in producing light (See abstract, claim 17, column 23, lines 17, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody in the kit as taught by the '588 patent for the antibody that binds specifically to Fas ligand as taught by Takahashi *et al*, Suda *et al*, Harlow *et al* and Campbell *et al* for a kit comprising the Fas ligand monoclonal antibody for use in detecting a Fas ligand in a sample in the blood of patient with SLE as taught by Takahashi *et al*, Suda *et al*, Harlow *et al* and Campbell *et al* and the'588 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '588 patent teaches that a kit will allow for ease of use for the practitioner since all the necessary reagents are included in a kit as taught by the '588 patent (See abstract, claim 17, column 23, lines 17, in particular).

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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